Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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An internally validated prediction model for critical COVID-19 infection and intensive care unit admission in symptomatic pregnant women

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Condensation: Prediction of intensive care unit admission (ICU) and critical disease is possible using baseline characteristics and inflammatory markers in pregnant women with symptomatic COVID-19.

Short title: Prediction of critical COVID-19 in symptomatic pregnant women

AJOG at a Glance:

A. **Why was the study conducted**: Pregnant women are at increased risk of complications from COVID-19 and pregnancy specific risk estimation models are lacking.

B. **What are the key findings:** The mini-model, including maternal age, body-mass index and pregnancy trimester can be used to estimate the risk of developing critical COVID-19 before disease onset (area under the receiver operating characteristics curve: 0.73). The addition of inflammatory markers at the time of diagnosis to maternal body-mass index (full-model) can accurately predict critical COVID-19 (area under the receiver operating characteristics curve: 0.85), preeclampsia and progression time from diagnosis to clinical deterioration.

C. **What does this study add to what is already known:** This study builds practical tools for risk estimation that can be used to inform the risk of progression to crticical COVID-19 along with maternal death, development of preeclampsia and time to clinical deterioration .

Keywords: prediction, SARS-CoV-2, vaccination, risk estimation, pregnancy, calibration

ABSTRACT

Background: Pregnant women are at increased risk of mortality and morbidity due to coronavirus disease 2019 (COVID-19). Many studies reported on the association of COVID-19 with pregnancy specific adverse outcomes but prediction models utilizing large cohort of pregnant women are still lacking for estimating the risk of maternal morbidity and other adverse events.

Objective: The main aim of this study was to develop a prediction model to quantify the risk of progression to critical COVID-19 and intensive care unit admission in pregnant women with symptomatic infection.

Study design: This was a multicenter retrospective cohort study including eight hospitals from four countries (UK, Austria, Greece and Turkey). Data extraction was from February 2020 until May 2021. Included were consecutive pregnant and early postpartum women (within 10 days of birth), reverse transcriptase polymerase chain reaction confirmed SARS-CoV-2 infection. The primary outcome was progression to critical illness requiring intensive care. Secondary outcomes included maternal death, preeclampsia and stillbirth. The association between the primary outcome and 12 candidate predictors with known association with severe COVID-19 in pregnancy, was analyzed with log-binomial mixed-effects regression and reported as adjusted risk ratios (aRR). All potential predictors were evaluated in one model and only baseline factors in another. Predictive accuracy were assessed by the area under the receiver operating characteristic curves (AUROC).

Results: Of 793 pregnant women positive for SARS-CoV-2 and symptomatic, 44 (5.5%) were admitted to intensive care, of whom 10 died (1.3%). The ‘mini-COvid Maternal Intensive Therapy’ model included demographic and clinical variables

available at disease onset: maternal age (aRR: 1.45, 95% CI: 1.07–1.95, P=0.015); body-mass index (aRR: 1.34, 95% CI: 1.06–1.66, P=0.010); and diagnosis in the third trimester of pregnancy (aRR: 3.64, 95% CI: 1.78–8.46, P=0.001). The optimism-adjusted AUROC was 0.73. The 'full-COvid Maternal Intensive Therapy' model included body-mass index (aRR: 1.39, 95% CI: 1.07–1.95, P=0.015), lower respiratory symptoms (aRR: 5.11, 95% CI: 1.81–21.4, P=0.007), neutrophil/lymphocyte ratio (aRR: 1.62, 95% CI: 1.36–1.89, P<0.001); and serum C-reactive protein (aRR: 1.30, 95% CI: 1.15–1.44, P<0.001), with an optimism-adjusted AUROC 0.85. Neither model showed signs of poor fit (P>0.05). Categorization as high risk by either model was associated with a shorter diagnosis to ICU admission interval (log-rank test P<0.001, both), higher maternal death (5.2% vs. 0.2%; P<0.0001) and preeclampsia (5.7% vs. 1.0%; P=0.0003). A spreadsheet calculator is available for risk estimation.

Conclusion: At presentation with symptomatic COVID-19, pregnant and recently postpartum women can be stratified into high and low-risk for progression to critical disease, even where resources are limited. This can support the nature and place of care. These models also highlight the independent risk for severe disease associated with obesity, and should further emphasize that even in the absence of other co-morbidities, vaccination is particularly important for these women. Finally, the model also provides useful information for policy makers when prioritizing national vaccination programmes to quickly protect those at highest risk of critical and fatal COVID-19.

INTRODUCTION

The presentation of coronavirus disease 2019 (COVID-19) is quite variable, ranging from asymptomatic infection to mild respiratory illness with minimal supportive care, to hospitalization with multi-organ failure and death [1,2]. Given alterations in physiology and immune function (e.g., inflammatory or prothrombotic markers) that may mask or predispose to severe-critical disease, pregnant women represent a unique population compared to their non-pregnant peers [3].

To reduce the burden on healthcare resources and focus them on those in greatest need, it is important to identify individual patients at increased actuarial risk of progression to critical COVID-19. Several COVID-related outcome prediction models, based on clinical, laboratory and imaging criteria, have been developed for the general population [4-6]. However, they have methodological limitations and do not account for pregnancy, limiting their generalizability and applicability [7]. Furthermore, some models rely heavily on radiologic investigations that are less frequently employed in pregnancy, particularly when symptoms are mild.

Emerging data from the United Kingdom and United States suggest that pregnant women may be experiencing more severe illness in the second wave of the pandemic compared with the first [8,9]. A recent living systematic review of maternal and fetal outcomes in pregnant women found that, although these women are less likely to report symptoms of COVID-19, they are more than twice as likely as their non-pregnant peers to require critical care or mechanical ventilation [3], a finding corroborated by large national registries such as Central for Disease Control (CDC) [9].

The main aim of this study was to develop a prediction model to quantify the risk of progression to critical COVID-19 in pregnant women with symptomatic infection, to

enable evidence-based triage and effective targeting of diagnostic and therapeutic interventions, including place of care.

MATERIALS AND METHODS

This was a multicenter cohort study including the following seven centers in four countries (Table S1). Data extraction was from the start of the pandemic in each country to 1st of May 2021. Relevant data were extracted from electronic patient records and anonymized for statistical analysis.

The inclusion criteria were pregnant and early postpartum women (within 10 days of birth), reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection. Included women had mild, moderate or severe illness at the time of diagnosis. The exclusion criteria were asymptomatic infection (positive RT-PCR for SARS-CoV-2 without any clinical symptoms); critical illness at the time of diagnosis; prior COVID-19 infection; or been vaccinated against SARS-CoV-2. All included women were either followed up as outpatients or admitted as an inpatient for supportive care. Women without critical illness or outpatients were followed-up for 14 days following the diagnosis of COVID-19. Patients were managed according to local protocols.

Symptomatic RT-PCR-positive pregnant/postpartum women but without lower respiratory tract symptoms (e.g., dyspnea) or abnormal chest imaging (i.e., tomography, lung ultrasound, or chest X-ray) were classified as having mild illness. Moderate illness was diagnosed in RT-PCR-positive pregnant/postpartum women with lower respiratory tract symptoms without significant hypoxia (pulse oximetry saturation ≥94%). Severe illness was diagnosed in RT-PCR-positive pregnant/postpartum women with oxygen saturation <94%, respiratory rate >30 breaths per minute, partial pressure of oxygen to fraction of inspired oxygen <300mmHg, but not meeting the criteria for critical illness. Critical illness was diagnosed in patients with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation support, septic

shock, cardiac dysfunction, hyper-inflammatory syndrome, or other organ system dysfunction [1].

Data on maternal age, self-reported ethnicity, body mass index (BMI), smoking, chronic co-morbidities (pregestational diabetes, chronic hypertension, heart disease [valvular, arrhythmia or cardiomyopathy] and bronchial asthma), gestational age at diagnosis, number of fetuses, and hospitalization were collected. When available, complete blood count (CBC) and C-reactive protein (CRP) assessment at the time of diagnosis were also collected. We did not collect data related to gestational diabetes due to variability in screening and diagnosis between centers. Candidate variables were selected among the factors with known or plausible associations with severe COVID-19 in pregnant and non-pregnant adult populations.

The primary outcome was progression to critical illness requiring intensive care unit (ICU) admission. Secondary outcomes were maternal death, preeclampsia and stillbirth. Preeclampsia was defined according to the revised criteria of the International Society for the Study of Hypertension in Pregnancy 2014 Statement [10]; hypertension was defined as new-onset systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, on two occasions more than 24 hours apart. Proteinuria was defined as a protein/creatinine ratio ≥30mg/mmol or a 24-hour urine collection with ≥300mg/24 hours. Stillbirth was defined as fetal death at or beyond 24^{+0} weeks' gestation.

A prediction model was developed and reported as a Type 1b analysis, which uses all available data for model building with interval validation procedures, as per the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [11]. This is the preferred method of prediction model building when sample size does not allow dataset partitioning. Moreover, some authors

have proposed that the TRIPOD 1b analysis is the preferred method of model building regardless of the sample size [12]. Our sample size was 690 women, based on: the need for intensive care in 8.7% of pregnant women with COVID-19 [13], having at least 10 patients with the primary outcome per tested variable, and the ability to test at least six variables (50% of the candidate pool) at the same time in a multivariable model. The literature suggests at least 10 adverse outcomes per tested variable to avoid model overfitting [14,15].

Ethics approval was obtained from Koc University Institutional Review Board (2021.264.IRB1.089), which allowed use of anonymized patient data without individual consent. Approvals were also obtained from National Health Services Health Research Authority and University of Vienna (2306/2020) and Athens. Participating centers were Attikon University Hospital (Athens, Greece), Koc University Hospital (Istanbul, Turkey), Medeniyet University Hospital (Istanbul, Turkey), Prof. Dr. Cemil Tascioglu City Hospital (Istanbul, Turkey), Sancaktepe Education and Research Hospital (Istanbul, Turkey), St. George's University Hospital (London, United Kingdom), and Vienna University Hospital (Vienna, Austria). All are tertiary care facilities with advanced life-support capabilities. The number of cases collected from each center, and previous publications, including the cases from each center, are summarized in Supplementary Table 1.

Statistical analysis

Continuous variables are presented as mean and standard deviation or median and interquartile range according to the distribution characteristics. The distribution of continuous variables was assessed with quartile-quartile plots, skewness and kurtosis

values. Group comparisons were made using t-test, Wilcoxon signed rank test, chi-squared test or Fisher's exact test, where appropriate.

Effect size was reported as mean, median difference or odds ratio (OR) and 95% confidence intervals (CI). Association of variables with ICU admission was analyzed with log-binomial mixed-effects regression and reported as adjusted risk ratios (aRR). Risk estimates in the regression were reported for one standard unit change in the respective variables. Random intercepts were used to account for study center-level variance.

Prediction models were built using generalized linear models using logit link function. Two predictive models were constructed from candidate predictors associated with more severe COVID-19 in or outside pregnancy. The first model used demographic and clinical variables available at disease onset (miniCOMIT, COvid Maternal Intensive Therapy). The second model used all variables, including those from investigations in hospital (fullCOMIT). Models were built using complete case data for each dataset (full and laboratory parameters available) while ensuring that the proportion of omitted cases did not surpass 1% of all available cases in each dataset. Akaike Information Criterion was used to assess model fit and meaningful improvements at each model iteration. Linearity assumptions were tested using the Box-Tidwell test and non-parametric transformation of continuous scale variables were tested for model improvement. Predictive capabilities and change in model fit were considered during the addition or subtraction of a variable. We aimed to achieve the most parsimonious model without sacrificing predictive capability or goodness of fit, using the Hosmer-Lemeshow test. Predictive capabilities were assessed by area under the receiver operating characteristic curves (AUROC). Optimism-adjusted AUROC values were obtained with repeated k-fold cross validation. Predictive accuracy measures, including

sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as positive and negative likelihood ratios (LR) were reported.

Model performances for each of miniCOMIT and fullCOMIT were assessed by three methods. First, calibration curves comparing expected and observed outcome rates by deciles of risk. Second, risk stratification tables by risk quintile. Third, Youden index cut-offs that maximized sensitivity and specificity were calculated for each model, to categorize women into high risk and low risk groups. The interval between diagnosis and ICU admission were compared for risk strata in each model by log-rank tests, and those pregnant/postpartum women not admitted to the ICU at the end of the follow-up period (14 days) were considered censored. The interval was tested to see whether classification allowed for a clinically meaningful interval, in which interventions can be applied. All analyses were conducted using R Software for Windows (Version 4.0.3).

RESULTS

Of 793 pregnant/postpartum women who were positive for SARS-CoV-2 by RT-PCR and symptomatic, 44 (5.5%) women were admitted to ICU, of whom 10 died (1.3%).

Table S2 shows that many baseline characteristics varied between women admitted to ICU versus those who were not. Women admitted to ICU were significantly older, and just over (vs under) 30 years of age. They were more often obese (one-third) and smokers (almost 7%). There were no differences in either ethnicity (most women overall were White) or chronic morbidities. Women admitted to ICU were at a more advanced gestational age (by just over three weeks), more likely to be in their third trimester and have lower respiratory tract symptoms. Most women had singleton pregnancies. There were 658 women (83.0%) who had laboratory assessment with CBC and serum CRP at diagnosis with COVID-19. Women admitted to the ICU (vs. those who were not) had significantly higher absolute neutrophil counts, lower lymphocyte counts, and higher neutrophil/lymphocyte ratios, in addition to higher CRP. Most women who were not admitted to ICU were still hospitalized.

Table 1 shows that by univariable regression analysis, all of the following were associated with ICU admission ($p<0.05$): clinical characteristics of maternal age, BMI, smoking, chronic co-morbidities, gestational age at diagnosis of COVID-19, third trimester pregnancy, and lower respiratory tract symptoms; and laboratory test results showing anemia, lymphopenia, higher neutrophil/lymphocyte ratio and higher CRP levels.

The miniCOMIT model (based on N=786 women, 7 excluded for missing data for one or more of the variables in the model) included maternal age (aRR: 1.45 [95% confidence interval: 1.07–1.95], P=0.015), BMI (aRR: 1.34 [1.06–1.66], P=0.010) and

third trimester of pregnancy (aRR: 3.64 [1.78–8.46], P=0.001) (Table 2). No significant interaction between the variables were detected. The optimism adjusted AUROC was 0.73 (Figure 1). By the Youden index cut-off, 362/786 (46.1%) of women were at high-risk and 424/786 (53.9%) at low-risk of needing ICU admission. The model had acceptable goodness of fit according to Hosmer-Lemeshow test (P=0.208) and had acceptable calibration (Figure S1). Risk stratification with quintiles of risk has shown an incremental change in ICU admission risk with each quintile (Table 3). The ICU admission risk was 2.0%, 8.7%, 13.3% and 27.3% for the first, second, third and fourth quintile and the trend was statistically significant (Cochrane-Armitage P<0.0001). Predictive accuracy parameters are presented in Table 3. Women at high risk according to Youden-index cut-off (vs. low risk) were more likely to require ICU admission (38/362, 10.5% vs. 6/424, 1.4%; P<0.001) and suffer maternal death (8/362, 2.2% vs. 2/424, 0.5%; P=0.030). They had a shorter diagnosis to ICU admission interval (log-rank test P<0.001, Figure 2a). However, preeclampsia did not significantly differ by risk category (10/362, 2.8% vs. 7/424, 1.6%; P=0.285) and there were few stillbirths (3/362, 8 per 1000 vs. 2/424, 5 per 1000).

The fullCOMIT model (based on N=658 women with available laboratory data) included BMI (aRR: 1.39 [1.07–1.95], P=0.015), lower respiratory tract symptoms of COVID-19 (aRR: 5.11 [1.81–21.4], P=0.007), neutrophil/lymphocyte ratio (aRR: 1.62 [1.36–1.89], P<0.001) and CRP levels (aRR: 1.30 [1.15-1.44], P<0.001) (Table 2). No significant interaction between the variables was detected. The optimism-adjusted AUROC was 0.85. By the Youden index cut-off, 174/658 (26.4%) of women were at high-risk and 484/658 (73.6%) at low-risk of needing ICU admission. The model had acceptable goodness of fit according to Hosmer-Lemeshow test (P=0.393) and had acceptable calibration (Figure S2). The ICU admission risk was 1.3%, 8.8%, 19.0% and 23.8%

and 81.8% for the first, second, third, fourth and fifth quintiles, respectively and the trend was statistically significant (Cochrane-Armitage P<0.0001, Table 3). Women at high risk according to Youden-index cut-off (vs. low risk) were more likely to require ICU admission (34/174, 19.5% vs. 7/484, 1.4%; P<0.0001) and had a shorter diagnosis to ICU admission interval (log-rank test P<0.001, Figure 2). These women more often suffered maternal death (9/174, 5.2% vs. 1/484, 0.2%; P<0.0001) or preeclampsia (10/174, 5.7% vs. 5/484, 1.0%; P=0.0003); there were few stillbirths (2/174, 11 per 1000 vs. 3/484, 6 per 1000). A spreadsheet calculator is available for both models for validation (Supplementary Material).

COMMENT

Principal findings

In this multicenter international prospective cohort study, we were able to identify women at increased risk of severe COVID-19, based on variables at symptom onset and particularly those at hospital admission. Risk stratification by either model was able to classify women into high- and low-risk categories with systematic differences in the rates of ICU admission, maternal death, and preeclampsia. fullCOMIT has good performance as a rule-out test for ICU admission (LR- ≤0.20), and both miniCOMIT and fullCOMIT have good and very good performances as rule-in tests once risks are estimated to be 10%-24.9%, respectively. High-risk women also had a shorter time from diagnosis to ICU admission. The predictive accuracy of fullCOMIT, based on all available variables, including laboratory tests in hospital (i.e., BMI, lower respiratory tract symptoms of COVID, neutrophil/lymphocyte ratio and CRP levels), was superior to miniCOMIT, based on variables available at symptom onset (i.e., maternal age, BMI and third trimester of pregnancy).

Results in the context of what is known

Prediction models are useful for informing patients about their risk and making individualized data-driven management decisions. Several prediction models have been proposed for use in non-pregnant adults with COVID-19 with varying success [4-6,16,17]. Most models utilized laboratory parameters at the time of diagnosis while some also incorporated imaging studies. A systematic review of published models criticized the optimistic prediction estimates and poor reporting [7]. Moreover, only two prediction models focused on pregnant women with COVID-19, based on very small cohorts (114 and 80 women) [18,19]. Tutiya et al. reported on a similar cohort to ours by including

symptomatic disease only, albeit with much smaller numbers (786 vs 114) [18]. They reported comorbidities such as asthma was associated with adverse outcomes, which was not the case in our study. Larger sample size may have allowed for better quantification of variance in our study. Tutiya et al. reported non-white ethnicity is a risk factor for severe COVID-19 [18]. We could not verify this finding but our cohort mainly consisted of Caucasian ethnicity (90%) but there was a two-fold increase in Black, Asian and ethnic minorities in the ICU admission cohort without statistical significance (RR: 2.22, 95% CI: 0.67 – 5.52). Although, we used most variables on a continuous scale, a linear increase in the risk observed in our cohort may not have external validity and better modeling approaches may exist in larger datasets. Recently, CDC data showed underweight individuals also are at increased risk of COVID-19 complications [20]. However, the risk increase showed a linear pattern above normal weight ranges, which is corroborated by our findings as well. Unfortunately, we did not have many underweight individuals in our cohort (0.4%) to reliably model the association.

We employed a large cohort of symptomatic women for whom a prediction model would be most useful. Our findings regarding the serum markers of inflammation and blood count parameters such as neutrophil/lymphocyte ratio are consistent with the published literature [16,17]. The miniCOMIT model incorporating only maternal and pregnancy characteristics had lower predictive accuracy compared to the results of Tutiya et al (AUROC: 0.73 vs. 0.82) [18]. However, we obtained optimism-adjusted AUC values, aimed for the most parsimonious model within the constraints of adverse outcome group size, and employed a much larger cohort. These points may have helped with avoiding overfitting, which is a significant issue for small cohorts and oversaturated models. Yao et al. reported a prediction model consisting of dyspnea, heart rate, respiratory rate, fever, CRP levels, and chest imaging [19]. The reported AUC

was very high (0.97), but the sample size was inadequate with only 50 patients in the development cohort and 30 patients in the validation.

We noted an increase in the prevalence of preeclampsia in the cohort predicted to be at high-risk of ICU admission and death by our model. Studies have reported an increased rate of preeclampsia in women with COVID-19 but did not demonstrate a link with COVID-19 severity [21]. Finally, the rate of stillbirth was twice as high in the group categorized as high risk for COVID-19, but this difference was not statistically significant. This finding is likely to be related to low numbers and inadequate statistical power, as larger studies demonstrated a two to three fold increase in stillbirth rates in women with COVID-19 [22]. Our results indicate that increased stillbirth rate may be explained by severe and critical COVID-19 infection in pregnant women. Validation of our models in larger cohorts may confirm this association between stillbirth and severe COVID-19.

Strengths and limitations

The strengths of our study include the large sample size of symptomatic pregnant women with COVID-19, adherence to recommended guidelines for model development, evaluating the independent contribution of recognized risk factors for severe COVID-19 (in and outside pregnancy) and including a simple-to-use spreadsheet calculator for external validation and clinical implementation.

Limitations do apply to our findings. First, we were probably underpowered to look at the impact of ethnicity (Black or other ethnic minority groups) or maternal comorbidities on maternal ICU admission with symptomatic COVID-19 infection. Second, being relatively underpowered resulted in no women being rated with a miniCOMIT risk ≥50%. Third, we did not include chest imaging (using ionizing radiation or alternatives

[23]) as a candidate predictor as it was not routinely included in management protocols in pregnancy, and we aimed to develop a generalizable model. However, the inclusion of imaging modalities would probably increase the predictive accuracy. Fourth, we did not perform external validation due to the constraints of our sample size. Dataset partitioning would have caused the model to overfit and yield biased estimates due to oversaturation. Instead, we opted to use the whole cohort for model building and adjusting for optimism via cross-validation, which is the recommended approach [11,12]. There are numerous international cohorts of pregnant women published in the literature, so external validation can be performed in future studies with relative ease[24,25]. Fifth, we did not account for treatments applied in each center in the model. However, only a limited number of therapeutic interventions have shown promise for halting progression to critical disease, and limited to no evidence is available for guiding treatment of pregnant women [26-29]. There is therefore little reason to assume that the inclusion of different treatment modalities would have impacted the performance of the fullCOMIT prediction model. Finally, we excluded asymptomatic cases so our findings would not apply to such women. However, asymptomatic infection has an excellent prognosis in pregnant women with COVID-19 and clinical applicability of a prediction model in such populations would be very limited[13].

Clinical and research implications

The fullCOMIT model can be used at the time of COVID-19 diagnosis in symptomatic pregnant women. Most trials excluded pregnant women and those who allowed participation had extremely small number of pregnancies to provide any direct evidence of benefit. Management of pregnant women with COVID-19 is an area currently supported by very little evidence. Therapeutic interventions, such as steroids, convalescent plasma and interleukin inhibitors, show some promise, particularly if

initiated early in the course of infection [26-28]. Compassionate use of these treatments in pregnant women is common practice in most settings. Our model successfully predicted the need for ICU admission and time interval between diagnosis and ICU admission, thereby identifying those women at increased risk of critical disease. This information could be useful to triage pregnant women with symptomatic COVID-19, so that healthcare resources and potential therapeutic interventions can be focused on those who are likely to benefit most. Symptomatic women who contact the maternity/emergency services should be screened for urgent admission (miniCOMIT score >10%) and all others be asked to attend, but not as urgently, for blood work so that fullCOMIT can be used.

The miniCOMIT model can be used to inform pregnant women of their risk of developing critical COVID-19 if infected and symptomatic, however mild. In both models, obesity was an independent predictor of severe COVID-19, as assessed by ICU admission.

Vaccination of pregnant women is of particular importance as pregnant women are at increased risk of severe COVID-19 compared to their non-pregnant peers and unvaccinated peers [9,30]. Vaccine hesitancy is a key challenge in pregnant women who are concerned about the risks of any vaccine not just to themselves, but also to their unborn infant. The use of this model to provide an individualized risk assessment for critical COVID-19 can support pregnant women to make more informed decisions around vaccination. This model will also be very useful for healthcare policy makers and vaccine program directors. Although COVID-19 vaccines appear safe and effective in eliciting an immune response in pregnant women, the number needed to vaccinate to prevent a case of severe COVID-19 is very high in young populations. The use of this baseline characteristics prediction model will enable the vaccine

program to prioritize those pregnant women at greatest risk. Targeted prioritization for vaccination will be of key importance in all countries around the world, not just in the current vaccine roll out, but also for future iterations of the vaccine directed at new variants of the virus. This will be essential in settings and populations where the availability of a suitable vaccine or the infrastructure to support a rapid mass vaccination program may be limited.

Nevertheless, external performance of these prediction models is very important for all clinical applications, and future studies should validate our findings. Moreover, our findings related to increased risk of other adverse outcomes, such as preeclampsia, in the high-risk group require further investigation. The improved predictive capability of fullCOMIT stemmed from inflammatory markers and the relationship between hyper inflammatory state in COVID-19, hypertension development and stillbirth should be evaluated in future studies.

Conclusions

We propose two prediction models for use in pregnant women with symptomatic COVID-19 that accurately predicted ICU admission and maternal death. A practical calculator is available for external validation and clinical application. fullCOMIT includes baseline characteristics and biochemical markers and can aid the focusing of medical resources on those most in need, while miniCOMIT includes baseline and pregnancy risk factors and can support pregnant women in their decision around whether or not to accept vaccination, as well as enable policy makers to prioritize at-risk pregnant women during the current and future COVID-19 vaccination programs.

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None

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31.

Table 1. Univariable binomial regression analysis of factors associated with intensive care unit (ICU) admission.

Variables	**Risk ratio (95% CI)[a]**	***P value***
Maternal and pregnancy specific variables		
Maternal age in years	1.51 (1.13 – 2.02)	0.0046
Body mass index in kg/m^2	1.46 (1.16 – 1.78)	0.0004
Body mass index > 30 kg/m^2	2.47 (1.30 – 4.51)	0.0039
Ethnicity		
– Caucasian	Reference	
– Black, Asian or Minority Ethnicity	2.22 (0.67 – 5.52)	0.127
Smoker	3.79 (0.92 – 10.4)	0.0258
Chronic comorbidity	1.92 (0.97 – 3.59)	0.0479
– Pre-pregnancy diabetes	3.38 (0.55 – 10.9)	0.0921
– Chronic hypertension	2.02 (0.11 –9.27)	0.485
– Heart disease	NE	NA
– Asthma	2.04 (0.61 – 5.07)	0.173
Gestational age at diagnosis in weeks	3.04 (1.33 – 8.31)	0.0165
Third trimester pregnancy	3.84 (1.88 – 8.90)	0.0005
Multiple gestation	2.56 (0.62 – 7.04)	0.115
Laboratory and disease specific variables available at the time of diagnosis		
Lower respiratory tract symptoms of COVID-19	8.23 (3.00 – 33.9)	0.0004
Hemoglobin levels in g/dL	0.77 (0.58 – 1.04)	0.083
Anemia (Hemoglobin <10 g/dL)	2.96 (1.48 – 5.60)	0.0012
Lymphocyte count (x 10^9/L)	0.40 (0.24 – 0.62)	0.0001
Lymphopenia (lymphocyte count <1000/mm^3)	2.60 (1.40 – 4.83)	0.0022
Absolute neutrophil count (x 10^9/L)	1.73 (1.35 – 2.19)	<0.0001
Neutrophil/lymphocyte ratio	1.42 (1.28 – 1.54)	<0.0001
CRP levels (mg/L)	1.38 (1.25 – 1.50)	<0.0001

[a] Log-binomial regression. Risk ratios correspond to one standard unit change in respective variables.

CRP: C-reactive protein, COVID-19: coronavirus disease 2019, NE: not estimable, NA: not applicable

Table 2. Multivariable log-binomial regression analysis of factors associated with intensive care unit (ICU) admission. miniCOMIT was built from variables available prior to diagnosis and fullCOMIT was built using all variables available at the time of diagnosis.

Multivariable regression	**Adjusted risk ratio (95% CI)[a]**	***P value***
miniCOMIT *(optimism adjusted AUC: 0.73)*		
– Maternal age in years	1.45 (1.07 – 1.95)	0.015
– Maternal body mass index in kg/m^2	1.34 (1.06 – 1.66)	0.010
– Third trimester of pregnancy	3.64 (1.78 – 8.46)	<0.001
fullCOMIT *(optimism adjusted AUC: 0.86)*		
– Maternal body mass index in kg/m^2	1.39 (1.09 – 1.71)	0.003
– Lower respiratory symptoms of COVID-19	5.11 (1.81 – 21.4)	0.007
– Neutrophil/lymphocyte ratio	1.62 (1.36 – 1.89)	<0.001
– CRP levels (mg/L)	1.30 (1.15 – 1.44)	<0.001

[a] Log-binomial regression. Risk ratios correspond to one standard unit change in respective variables.

AUC: Area under the curve, CI: confidence interval, CRP:C-reactive protein, COMIT: COvid Maternal Intensive Therapy, COVID-19: coronavirus disease 2019

Table 3. Risk stratification table using five groups of predicted probability. Predictive values are presented as mean (95% confidence intervals).

Predicted risk	Women in range	ICU admission	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Mini-COMIT								
<5%	454	9 (2.0%)	79.5% (64.7 – 90.2%)	59.9% (56.3 – 63.5%)	10.5% (9.0 – 12.3%)	98.0% (96.4 – 98.8%)	1.99 (1.67 – 2.36)	0.34 (0.19 – 0.61)
5 to 9.9%	231	20 (8.7%)	34.0% (20.4 – 49.9%)	88.4% (85.8 – 90.6%)	14.8% (9.9 – 21.5%)	95.7% (94.8 – 96.5%)	2.94 (1.86 – 4.64%)	0.75 (0.60 – 0.92)
10 to 24.9%	90	12 (13.3%)	6.8% (1.4 – 18.6%)	98.9% (97.9 – 99.5%)	27.3% (9.3 – 57.7%)	94.9% (94.5 – 95.3%)	6.58% (1.4 – 18.7%)	0.94 (0.87 – 1.02)
25 to 49.9%	11	3 (27.3%)	0.0% (0.0 – 8.0%)	100.0% (99.5 – 100.0%)	–	94.4% (94.4 – 94.4%)	–	1.0 (1.0 – 1.0)
≥50	0	0 (0.0)	–	–	–	–	–	–
Full-COMIT								
<5%	461	6 (1.3%)	85.3% (70.8 – 94.4%)	73.7% (70.0 – 77.2%)	17.7% (15.2 –20.6%)	98.7% (97.3– 99.4%)	3.25 (2.71 – 3.90)	0.20 (0.09 – 0.42)
5 to 9.9%	102	9 (8.8%)	70.0% (55.4 – 82.1%)	88.8% (86.0 – 91.1%)	33.6% (27.5 – 40.3%)	97.3% (95.9% – 98.2%)	6.23 (4.70 – 8.34)	0.34 (0.22 – 0.52)
10 to 24.9%	63	12 (19.0%)	34.1% (20.0 – 50.5%)	97.0% (95.4 – 98.2%)	43.7% (29.4 – 59.1%)	95.6% (94.6 – 96.5%)	11.7 (6.28 – 21.8)	0.68 (0.54 – 0.85)
25 to 49.9%	21	5 (23.8%)	21.9% (10.5 – 37.6%)	99.6% (98.8 – 99.9%)	81.8% (50.1 – 95.3%)	95.0% (94.2 – 95.7%)	67.7 (15.1 – 303.2)	0.78 (0.67 – 0.91)
≥50	11	9 (81.8%)	0.0% (0.0% –8.6%)	100.0% (99.4 – 100.0%)	–	93.7% (93.7 – 93.7%)	–	1.0 (1.0 – 1.0)

Sensitivity, specificity, and predictive values calculated using the upper limit of the risk range to define a positive test.

CI: confidence interval, LR: likelihood ratio, NPV: negative predictive value, PPV: positive predictive value, COMIT: COvid Maternal Intensive Therapy, ICU: intensive care unit admission

Figure 1. Receiver operating characteristics curves of mini-COMIT (green line) and full-COMIT (orange line). Full-COMIT, using laboratory parameters, body mass index and respiratory symptoms outperformed mini-COMIT, which includes maternal age, body mass index and gestational age.

Figure 2. Diagnosis to intensive care unit (ICU) admission interval stratified by risk categories according to mini-COMIT (a) and full-COMIT (b). Risk stratification by both models was significantly associated with the diagnosis to ICU admission interval (log-rank test P<0.0001, both).

Figure S1. Calibration plot of miniCOMIT. The smooth black line represents fit of the model predicted risk of outcome to the observed rate within each decile of predicted probability. The straight red line is used as reference for perfect fit. The bar chart at the base of the figure presents distribution of cases with intensive care unit admission (above the line) across the spectrum of predicted probability.

Figure S2. Calibration plot of fullCOMIT. The smooth black line represents fit of the model predicted risk of outcome to the observed rate within each decile of predicted probability. The straight red line is used as reference for perfect fit. The bar chart at the base of the figure presents distribution of cases with intensive care unit admission (above the line) across the spectrum of predicted probability.

Supplementary Table 1. Patients included from each center and previous publications including patients from the same cohort.

Center	Sample size	Previous publications with overlap
Koc University, School of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey and American Hospital	30	None
Sancaktepe Sehit Prof Dr Ilhan Varank Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey	530	Kuzan TY, Murzoğlu Altıntoprak K, Çiftçi HÖ, Kuzan BN, Yassa M, Tuğ N, Çimşit NÇ. Clinical and radiologic characteristics of symptomatic pregnant women with COVID-19 pneumonia. J Turk Ger Gynecol Assoc. 2021 Feb 26. doi: 10.4274/jtgga.galenos.2021.2020.0215. Epub ahead of print. PMID: 33631874. Yassa M, Yassa A, Yirmibeş C, Birol P, Ünlü UG, Tekin AB, Sandal K, Mutlu MA, Çavuşoğlu G, Tug N. Anxiety levels and obsessive compulsion symptoms of pregnant women during the COVID-19 pandemic. Turk J Obstet Gynecol. 2020 Sep;17(3):155-160. doi: 10.4274/tjod.galenos.2020.91455. Epub 2020 Oct 2. PMID: 33072418; PMCID: PMC7538825. Tug N, Yassa M, Köle E, Sakin Ö, Çakır Köle M, Karateke A, Yiyit N, Yavuz E, Birol P, Budak D, Kol Ö, Emir E. Pregnancy worsens the morbidity of COVID-19 and this effect becomes more prominent as pregnancy advances. Turk J Obstet Gynecol. 2020 Sep;17(3):149-154. doi: 10.4274/tjod.galenos.2020.38924. Epub 2020 Oct 2. PMID: 33072417; PMCID: PMC7538816. Kalafat E, Yassa M, Koc A, Tug N; TULIP collaboration. Utility of lung ultrasound assessment for probable SARS-CoV-2 infection during pregnancy and universal screening of asymptomatic individuals. Ultrasound Obstet Gynecol. 2020 Oct;56(4):624-626. doi: 10.1002/uog.23099. PMID: 32916004.

Istanbul Medeniyet University, Faculty of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey	44	None
Istanbul Provincial Health Directorate, Prof Dr. Cemil Tascioglu City Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey	70	None
Fetal Medicine Unit, St George's Hospital, St George's University of London, UK.	40	Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Brocklehurst P, Kurinczuk JJ; UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020 Jun 8;369:m2107. doi: 10.1136/bmj.m2107. PMID: 32513659; PMCID: PMC7277610.
Department of Obstetrics and feto-maternal Medicine, Medical University of Vienna, Vienna, Austria	43	None
Attikon University Hospital, University of Athens, 3rd Department of Obstetrics and	36	None

Gynecology, Athens, Greece		

Table S2. Baseline characteristics and laboratory parameters of pregnant women with symptomatic COVID-19, stratified according to intensive care unit (ICU) admission status

Variables	**SARS-CoV-2 positive women without ICU admission (n=749)**	**SARS-CoV-2 positive women with ICU admission (n=44)**	**Absolute mean, median difference (95% CI) [a]**	***P value*** **[b]**
Maternal and pregnancy variables				
Maternal age in years	29.4 ± 5.68	32.0 ± 5.70	2.59 years (0.81 – 4.37 years)	0.0051
Body mass index in kg/m^2	25.7 (23.8 – 28.5)	28.0 (25.3 – 31.2)	2.28 kg/m^2 (2.00 – 2.60 kg/m^2)	0.0006
Body mass index >30 kg/m^2	136 (18.1)	16 (36.4)	18.5% (4.2 to 32.9%)	0.0038
Smoker	12 (1.6)	3 (6.8)	5.2% (-2.2 to 12.6%)	0.023
Ethnicity				0.117
– Caucasian	717 (95.7)	40 (90.9)	-5.1% (-7.9 – -2.0%)	
– Afro-Caribbean	21 (2.8)	4 (9.1)	6.3% (-2.2 – 14.9%)	
– Asian	9 (1.2)	0 (0.0)	-1.2% (-2.0 – -0.4%)	
– Not reported	2 (0.3)	0 (0.0)		
Chronic comorbidity (one/more)	49 (6.5)	6 (13.6)	7.1% (-3.1 to 17.3%)	0.079
– Pre-pregnancy diabetes	9 (1.2)	2 (4.5)	3.4% (-2.8 – 9.6%)	
– Chronic hypertension	8 (1.1)	1 (2.3)	1.2% (-0.9 to 2.9%)	
– Heart disease	3 (0.4)	0 (0.0)	-0.4% (-0.8 – 0.5%)	
– Bronchial asthma	33 (4.4)	4 (9.1)	4.7% (-0.4 – 13.4%)	
Gestational age at diagnosis in weeks	27.8 (20.0 – 34.4)	29.5 (27.4 – 34.1)	3.22 (1.38 – 8.99)	0.014
– First trimester	82 (10.9)	0 (0.0)	-10.9% (-12.7 – -9.2%)	
– Second trimester	260 (34.7)	8 (18.2)	-19.7% (-27.4 – -12.1%)	
– Third trimester	400 (53.4)	36 (81.8)	28.2% (16.8 – 39.7%)	

– Postpartum	7 (1.0)	0 (0.0)		
Multiple gestation	19 (2.5)	3 (6.8)	4.3% (-3.2 – 11.8%)	0.107
Lower respiratory tract symptoms of COVID-19	454 (60.6)	41 (93.2)	32.5% (24.3 – 40.7%)	0.0002
Hospitalized for COVID-19	573 (76.5)	44 (100.0)	23.5% (20.4 – 26.6%)	0.0005
Laboratory variables at diagnosis				
Hemoglobin levels in g/dL	11.4 ± 1.36	11.0 ± 1.68	-0.39 (-0.94 – 0.15)	0.148
Lymphocyte count (x 10^9/L)	1.27 (0.96 – 1.72)	0.97 (0.69 – 1.20)	-0.30 (-0.36 – -0.23)	<0.0001
Absolute neutrophil count (x 10^9/L)	5.73 ± 2.41	7.59 ± 2.95	1.87 (0.92 – 2.82)	0.0002
Neutrophil/lymphocyte ratio	4.19 (2.93 – 5.91)	8.00 (5.40 – 13.8)	3.81 (3.63 – 4.00)	<0.0001
CRP levels (mg/L)	2.53 (0.71 – 8.00)	19.0 (10.5 – 63.1)	16.5 (16.1 – 17.0)	<0.0001

[a] Parametric or non-parametric bootstrapped confidence intervals are reported according to parent distribution
[b] *Wilcoxon signed rank, t-test, chi-squared test or Fisher's exact test where appropriate*

Continuous variables are presented as mean ± standard deviation or median and interquartile range according to distribution characteristics. Categorical variables are presented as number and percentage of total.

NE: non estimable, COVID-19: Coronavirus disease 2019, CRP: C-reactive protein.